PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classificati n 6 : A61K 9/14, 9/51

A1

(11) International Publication Number: WO 96/24336

(43) International Publication Date: 15 August 1996 (15.08.96)

(21) International Application Number: PCT/US96/01801

(22) International Filing Date: 8 February 1996 (08.02.96)

(30) Priority Data:
08/386,790 10 February 1995 (10.02.95) US

(71) Applicant: NANOSYSTEMS L.L.C. [US/US]; Building 1, 1250 South Collegeville Road, Collegeville, PA 19426 (US).

(72) Inventors: FRANSON, Nancy, M.; 144 Iron Bark Court, Collegeville, PA 19426 (US). SNYDER, Donald, R.; 129 Regal Court, Limerick, PA 19468 (US).

(74) Agents: WEST, Paul, B.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NSAID NANOPARTICLES

(57) Abstract

Dispersible particles consisting essentially of crystalline NSAID having hydroxypropyl cellulose adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 1000 nm. Pharmaceutical compositions containing the particles exhibit unexpectedly reduced gastric irritation following oral administration and/or hastened onset of action.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgystan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

NSAID nanoparticles

Field Of The Invention

This invention relates to pharmaceutical compositions containing NSAIDs used as analgesics for mammals.

Background of Invention

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used and therapeutically effective groups of drugs. However, gastric irritation problems constitute the most frequently recognized adverse side effect following oral administration of NSAIDs. Such side effects are well recognized and must be weighed against the clinical efficacy of the drugs.

A great amount of research has been undertaken in an attempt to understand the underlying mechanism responsible for these effects. For example, Cioli et al, Tox. and Appl. Pharm., 50, 283-289 (1979) suggest that gastrointestinal lesions in laboratory animals resulting from the oral administration of acidic NSAIDs may depend on two different mechanisms: a local action exerted by contact with the gastric mucosa and a generalized/centrally mediated (systemic) action, taking place following oral administration.

More recently, Price et al, Drugs 40 (Suppl. 5):1-11, 1990, suggest that NSAID-induced gastric damage occurs as a result of NSAID-mediated direct and indirect acidic damage followed almost simultaneously by the deleterious systemic effect of prostaglandin inhibition.

A variety of strategies have been used in the management of NSAID-induced gastric damage. These include: 1) the development and use of NSAIDs with

less toxic potential; 2) the reduction or elimination of the agent that actually causes the injury; and 3) the enhancement of the mucosal defense. However, these approaches have not proven entirely successful.

For example, the most effective means of preventing gastric damage, i.e., by eliminating the primary aetiological agent is rarely feasible with NSAIDs inasmuch as patients with severe inflammatory disease are rarely able to cease using these drugs. Although selection of less toxic NSAIDs should prove useful, the only practical solution, at present, is to treat the NSAID induced gastric damage. Misoprostol (a methylated prostaglandin E_1) has been approved by the FDS for use in preventing NSAID gastropathy. However, Misoprostol is expensive, must be administered multiple times daily and can cause unacceptable side effects.

In copending U.S. Application Serial Number 897,193 filed June 10, 1992, the use of NSAID particles having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 400 nm was described as being useful in reducing gastric irritation in mammals.

It would be highly desirable to provide NSAID formulations that can exhibit an even greater reduction in gastric irritation and exhibiting greater enhanced onset of action as an analgesic.

Summary of the Invention

It has been discovered that NSAID nanoparticles as described in U.S. Application Serial Number 897,193 when accompanied by hydroxypropyl cellulose as a surface modifier exhibits unexpectedly superior reduced gastric irritation following oral

administration as well as exhibiting hastened onset of analgesic activity.

More particularly, in accordance with this invention, there are provided particles consisting essentially of an NSAID having hydroxypropyl cellulose adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 1000 nm.

This invention further provides a pharmaceutical composition comprising the above-described particles and a pharmaceutically acceptable carrier.

In another embodiment of the invention, there is provided a method of treating a mammal comprising administering to the mammal the above-described pharmaceutical composition.

In yet another embodiment of the invention, there is provided a method of preparing the above-described particles comprising the steps of dispersing an NSAID in a liquid dispersion medium and wet grinding the NSAID in the presence of rigid grinding media, wherein the pH of said medium is maintained within the range of from 2 to 6.

In further embodiments of the invention, there are provided methods of reducing gastric irritation and/or hastening the onset of action which include administering the above-described pharmaceutical composition to a mammal.

It is an advantageous feature of this invention that pharmaceutical compositions containing NSAIDs are provided which exhibit reduced gastric irritation following oral administration.

It is another advantageous feature of this invention that pharmaceutical compositions are provided exhibiting hastened onset of action.

It is another advantageous feature of this invention that the use of the particular surface modifier reduces adsorption variability.

Other advantageous features will become readily apparent upon references to the following description of preferred embodiments.

Description of Preferred Embodiments

This invention is based on the discovery that nanoparticulates comprising an NSAID, for example naproxen, having its surface modified with hydroxypropyl cellulose demonstrates reduced gastric irritation and/or a more rapid onset of action following oral administration. While the invention is described herein primarily in connection with its preferred class of drugs, i.e., NSAIDs, it is also useful in conjunction with other classes of drug substances, e.g., antibiotics, quinolones, antilipemics and roentgenographics.

The particles of this invention comprise an NSAID. The NSAID exists as a discrete, crystalline phase. The crystalline phase differs from an amorphous or non-crystalline phase which results from conventional solvent precipitation techniques, such as described in U.S. Patent 4,826,689. The NSAID can be present in one or more suitable crystalline phase.

The invention can be practiced with a wide variety of NSAIDs. However, the NSAID must be poorly soluble and dispersible in at least one liquid medium. By "poorly soluble" it is meant that the NSAID has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably of

less than about 1 mg/ml at processing temperature, e.g., room temperature. The preferred liquid dispersion medium is water. However the invention can be practiced with other liquid media in which the NSAID is poorly soluble and dispersible including, for example, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane and glycol. The pH of the aqueous dispersion media can be adjusted by techniques known in the art.

The NSAIDs useful in the practice of this invention can be selected from suitable acidic and nonacidic compounds. Suitable acidic compounds include carboxylic acids and enolic acids. Suitable nonacidic compounds include, for example, nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine and dapsone.

Suitable carboxylic acid NSAIDs include, for example, salicylic acids and esters thereof, such as aspirin, diflunisal, benorylate and fosfosal; aceitc acids, including phenylacetic acids such as diclofenac, alclofenac and fenclofenac, and carbo-and heterocyclic acetic acids such as etodolac, indomethacin, sulindac, tolmetin, fentiazac and tilomisole; and propionic acids, such as carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acids, ibuprofen, naproxen, fenoprofen, indoprofen, pirprofen; and fenamic acids, such as flufenamic, mefenamic, meclofenamic and niflumic.

Suitable enolic acid NSAIDs include, for example, pyrazolones such as oxyphenbutazone, phenylbutazone, apazone and feprazone, and oxicams such as piroxicam, sudoxicam, isoxicam and tenoxicam.

The above-described NSAIDs are known compounds and can be prepared by techniques known in the art.

In particularly preferred embodiments of the invention, the NSAID is naproxen, hetoprofin, indomethacin or ibuprofen, and particularly naproxen.

The particles of this invention contain an NSAID as described above having a hydroxypropyl cellulose adsorbed on the surface thereof.

I have discovered that hydroxypropyl cellulose, particularly hydroxypropyl cellulose having a viscosity range of 1 to 100 cps in a 3% solution in water preferably the viscosity to about 10 cps when used as a surface modifier for NSAIDs, in formulating nanoparticulate compositions unexpectedly results in enhanced resistance to gastric irritation as compared to that of other surface modifiers described in U.S. Application Serial Number 897,193. This particular property of the species of the genus of U.S. Application Serial Number 897,193 has been heretofore unknown.

The hydroxypropyl cellulose is adsorbed on the surface of the NSAID in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the NSAID or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages.

As used herein, particle size refers to a number average particles size as measured by conventional particles size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of less than about 1000 nm: is meant that at least 90% of the particles have a number average particle size of less than about

1000 nm when measured by the above-noted techniques. In preferred embodiments of the invention, the effective average particle size is less than about 400 nm. With reference to the effective average particle size, it is preferred that at least 95% and, more preferably, at least 99% of the particles have a particle size of less than the effective average, e.g., 400 nm. In particularly preferred embodiments, essentially all of the particles have a size less than 1000 nm.

The particles of this invention can be prepared in a method comprising the steps of dispersing an NSAID in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the NSAID to an effective average particle size of less than about 1000 nm. The particles can be reduced in size in the presence of the surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles of this invention is set forth below. The NSAID selected is obtained commercially and/or prepared by techniques known in the art in a conventional coarse form. It is preferred, but not essential, that the particle size of the coarse NSAID selected be less than about 100 µm as determined by sieve analysis. If the coarse particle size of the NSAID is greater than about 100 µm, then it is preferred that the particles of the NSAID be reduced in size to less than 100 µm using a conventional milling method such as airjet or fragmentation milling.

The coarse NSAID selected can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of the NSAID in the liquid medium can vary from about 0.1-60%, and

preferably is from 5-30% (w/w). It is preferred, but not essential, that the surface modifier be present in the premix. The concentration of the surface modifier can vary from about 0.1 to about 90%, and preferably is 1-75%, more preferably 20-60%, by weight based on the total combined weight of the drug substance and surface modifier. The apparent viscosity of the premix suspension is preferably less than about 1000 centipoise.

The premix can be used directly by subjecting it to mechanical means to reduce the average particle size in the dispersion to less than 1000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the NSAID and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation, e.g., a roller mill or a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a premilling dispersion step when a recirculating media mill is used for attrition.

The mechanical means applied to reduce the particle size of the NSAID conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the intended result, i.e., the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is from about 10 to about 1000 centipoise. For ball milling, the apparent viscosity of the premix preferably is from about 1 up to about 100 centipoise. Such ranges tend to afford an

optimal balance between efficient particle fragmentation and media erosion.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. However, polymeric grinding media and zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are believed to be acceptable for the preparation of pharmaceutical compositions. Further, other media, such as stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium, are expected to be useful. Preferred media have a density greater than about 2.5 g/cm^3.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. On the other hand, processing times of less than 1 day (residence times of one minute up to several hours) have provided the desired results using a high shear media mill.

The particles must be reduced in size at a temperature which does not significantly degrade the NSAID. Processing temperatures of less than about 30-40°C are ordinarily preferred. If desired, the processing equipment can cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at

processing pressures which are safe and effective for the milling process. For example, ambient processing pressures are typical of ball mills, attritor mills and vibratory mills. Processing pressures up to about 20 psi (1.4 kg/cm^2) are typical of media milling.

Milling must be carried out under acidic conditions, at a pH of from 2-6, preferably 3-5. The preferred pH depends, e.g., on the acidity and solubility of the particular NSAID selected. Acid resistant milling equipment is highly preferred, e.g., equipment fabricated of high grade stainless steel, e.g., grade 316 SS, or equipment coated with an acid resistant coating.

The surface modifier, it if was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed, e.g., by shaking vigorously. Optionally, the dispersion can be subjected to a sonication step, e.g., using an ultrasonic power supply. For example, the dispersion can be subjected to ultrasonic energy having a frequency of 20-80kHz for time of about 1 to 120 seconds.

The relative amount of the NSAID and surface modifier can vary widely and the optimal amount of the surface modifier can depend, for example, upon the particular NSAID and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the NSAID, etc. The surface modifier preferably is present in an amount of about 0.1-10 mg per square meter surface area of the NSAID. The surface modifier can be present in an amount of 0.1-90%, preferably 0.5-80%, and more preferably 1-60% by weight based on the total weight of the dry particle.

The resulting dispersion is stable and consists of the liquid dispersion medium and the above-described particles. The dispersion of surface modified NSAID nanoparticles can be spray coated onto sugar spheres or onto a pharmaceutical excipient in a fluid-bed spray coated by techniques well known in the art.

Pharmaceutical compositions according to this invention can include the composition described above and a pharmaceutically acceptable carrier therefor. Suitable pharmaceutically acceptable carriers are well known to those skilled in the art. These include non-toxic physiologically acceptable carriers, adjuvants or vehicles for parenteral injection, for oral administration in solid or liquid form, for rectal administration, and the like. A method of treating a mammal in accordance with this invention comprises the step of administering to the mammal in need of treatment an effective amount of the above-described pharmaceutical composition. The selected dosage level of the NSAID for treatment is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore, depends upon the particular NSAID, the desire therapeutic effect, on the route of administration, on the desired duration of treatment and other factors.

It is a particularly advantageous feature that the pharmaceutical compositions of this invention exhibit reduced gastric irritation and/or more rapid onset of action as illustrated in the example that follows.

Example

Example 1

Preparation 1

To 670 g of deionized water, 30 g of hydroxypropylcellulose (Klucel Type EF; Aqualon) was dissolved using a continuous laboratory mixer. 300 g of naproxen was dispersed into the HPC solution until a homogeneous suspension was obtained. A laboratory scale media mill filled with polymeric grinding media was used in a continuous fashion until the mean particle size was approximately 200 nm as measured by laser light scattering technique, ex. Microtrak UPA.

Preparation 2

The 30% w/w naproxen dispersion prepared above was spray dried to a dry powder form using a laboratory spray drier equipped with a rotary atomizer. The final powder consisted of particles in the size range of 20-40 micron diamter and a moisture content of approximately 0.3% by LOD. The powder was hand filled into size 00 gelatin capsules to a strength of 250 mg naproxen/capsule. 220 g of the spray dried material above was blended prepared with 44 g of croscarmellose sodium (Ac-Di-Sol) in a small twin shell blender. The material was passed through a roller compactor at 10 tons pressure and mill/sieve to approximately 16-40 mesh particle size. 134 g of lactose (hydrous) and 2 g of magnesium stearate was blended with the dry granulation for 15 minutes in a twin shell blender. The powder was compressed on a rotary tablet press to a final tablet weight of 400 mg and a hardness of 9-12 kp. Each tablet contained 200 mg of naproxen. The nanonaproxoflin was tested for adsorption time spiral co? tablets in fed dogs. The following was found.

Bioavailability Results in Fed Dogs

Formulation	Dose*	MAT**
Preparation 1	250	9
Preparation 2	250	11
Example 1	200	14
Anaprox Caplet (Syntex)	250	45
ALEVE Caplet (Proctor and Gamble)	200	40
Naproxsyn suspension (Syntex)	250	49

* mg of naproxen per dog

** MAT = mean-absorption time in minutes (n=4-9)

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

Claims

1. Particles consisting essentially of an NSAID having hydroxypropyl cellulose adsorbed on the surface thereof in an amount sufficient to maintain an average particle size of less than about 1000 nm.

2. The particles of claim 1 having an effective average particle size of less than 400 nm.

3. The particles of claim 1 wherein the hydroxypropyl cellulose is present in an amount of 0.2 to 90% by weight based on the total weight of the dry particle.

4. The particles of claim 1 wherein said NSAID is selected from nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenace, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisole, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, piroprofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylburzone, apazone and feprazone, piroxicam, sudoxicam, isoxicam and tenoxicam.

5. The particles of claim 1 wherein said NSAID is selected from naproxen, indomethacin and ibuprofen.

6. The particles of claim 5 wherein said NSAID is naproxen.

7. The particles of claim 1 wherein said hydroxypropyl cellulose has a viscosity range from 1 to 100 cps.

8. A pharmaceutical composition comprising the particles of claim 1 and a pharmaceutically acceptable carrier.

9. A method of treating a mammal comprising administering to the mammal an effective amount of the pharmaceutical composition of claim 1.

10. A method of reducing gastric irritation following oral administration to a mammal of a pharmaceutical composition comprising an NSAID, said method comprising administering said pharmaceutical composition in the form of particles consisting essentially of said NSAID having hydroxypropyl cellulose adsorbed thereon in an amount sufficient to maintain an average particle size of less than about 1000 nm.

11. A method of hastening onset of action following administration to a mammal of a pharmaceutical composition comprising an NSAID, said method comprising administering said pharmaceutical composition in the form of particles consisting essentially of said NSAID having hydroxypropyl cellulose adsorbed thereon in an amount sufficient to maintain an average particle size of less than about 1000 nm.

12. A method of preparing the particles of claim 1 comprising the steps of dispersing an NSAID and hydroxypropyl cellulose in a liquid dispersion medium and wet grinding said NSAID in the present of rigid grinding media to an effective average particle size of less than about 1000 nm, wherein the pH of said medium is maintained within the range of from 2 to 6 during said wet grinding.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 96/01801

A. CLASSIFICATION F SUBJECT MATTER
IPC 6 A61K9/14 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 25190 (STERLING WINTHROP INC.,U.S.A.) 23 December 1993 cited in the application see claims see page 5, line 27 ---	1-12
X	EP,A,0 499 299 (STERLING WINTHROP INC.,U.S.A.) 19 August 1992 see the whole document --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 June 1996	10.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/01801

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A,42 44 466 (PHARMATECH GMBH,DE) 30 June 1994 see claims see column 4, line 1 - line 10 see column 4, line 51 see column 5, line 11 see column 5, line 14 see example 2 see column 2, line 62 -----	1-12

2

INTERNATIONAL SEARCH REPORT

PCT/US 96/01801

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 9-11 are directed to a method of treatment of the human body by therapy (Rule 39.1 (iv) PCT), the search has been carried out and based upon the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inv onal Application No
PCT/US 96/01801

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9325190	23-12-93	AU-B-	4396493	04-01-94
		CA-A-	2118517	23-12-93
		EP-A-	0644755	29-03-95
		HU-A-	70952	28-11-95
		JP-T-	8501073	06-02-96
EP-A-499299	19-08-92	US-A-	5145684	08-09-92
		AU-B-	642066	07-10-93
		AU-B-	1014592	30-07-92
		AU-B-	654836	24-11-94
		AU-B-	1014792	30-07-92
		EP-A-	0498482	12-08-92
		IL-A-	100755	08-12-95
		JP-A-	4317053	09-11-92
		JP-A-	4295420	20-10-92
		US-A-	5451393	19-09-95
		US-A-	5494683	27-02-96
		US-A-	5399363	21-03-95
		US-A-	5318767	07-06-94
DE-A-4244466	30-06-94	EP-A-	0605933	13-07-94
		JP-A-	7053725	28-02-95